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(54) **Determining absorption coefficients or modified scattering coefficients**

(57) A method of determining the absolute absorption coefficient and the modified scattering coefficient in highly scattering medium, comprises passing light into the medium, detecting diffuse light leaving the medium, measuring changes in at least two of the intensity, phase and modulation depth that are induced in the light by a common cause such as by small absorption coefficient changes or changes in source/detector distance. These changes can be induced by a) changes in the chromophore concentration, b) small changes in wavelength, c) changes in blood flow and oxygenation in a limb or in the head of a foetus, or d) changes in the distance between light source and detector. The absorption coefficient may be determined from the ratio of the two measured changes.

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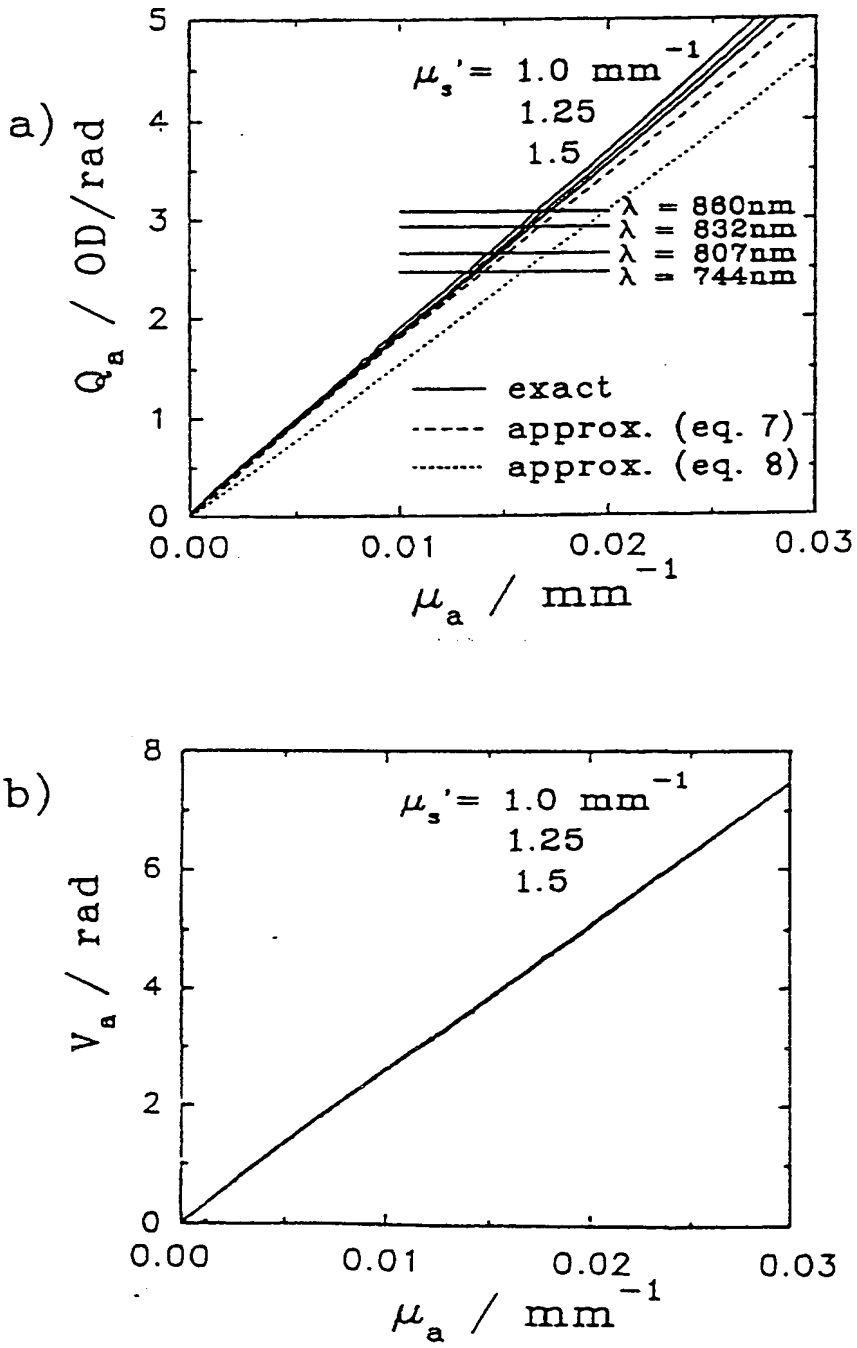
a)
Q_a / OD/rad
μ_s'= 1.0 mm^{-1}
1.25
1.5
λ = 860nm
λ = 832nm
λ = 807nm
λ = 744nm
exact
approx. (eq. 7)
approx. (eq. 8)
μ_a / mm^{-1}
b)
V_a / rad
μ_s'= 1.0 mm^{-1}
1.25
1.5
μ_a / mm^{-1}

Fig. 1

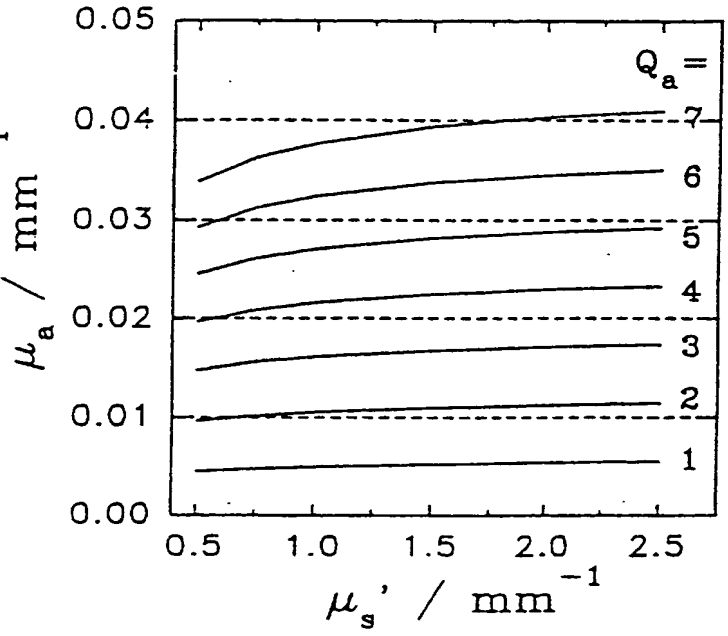

Fig. 2

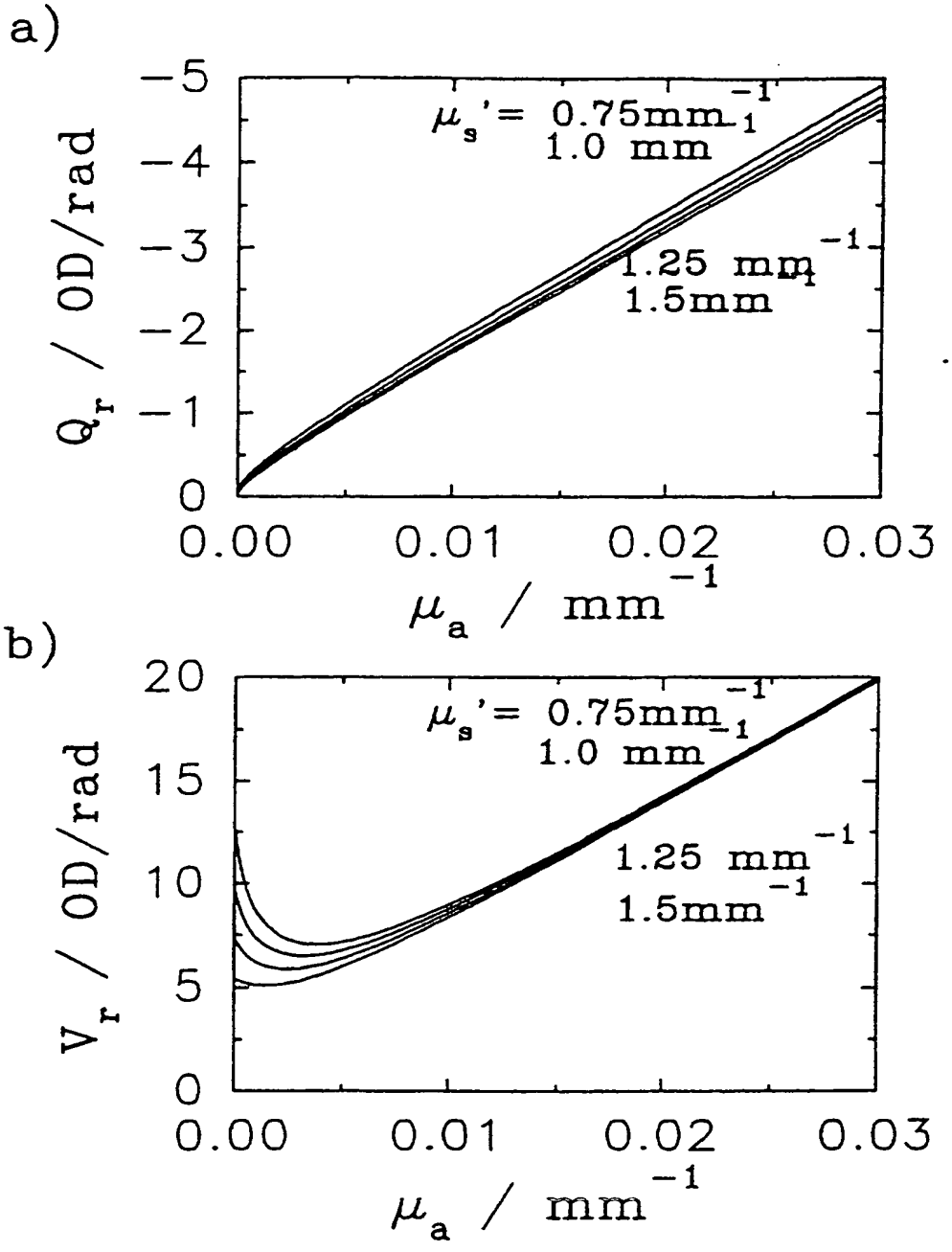
a)
$\mu_s' = 0.75 mm^{-1}$
1.0 mm
1.25 mm^{-1}
1.5mm
Q_r / OD/rad
μ_a / mm^{-1}
b)
$\mu_s' = 0.75 mm^{-1}$
1.0 mm
1.25 mm^{-1}
1.5mm^{-1}
V_r / OD/rad
μ_a / mm^{-1}

Fig. 3

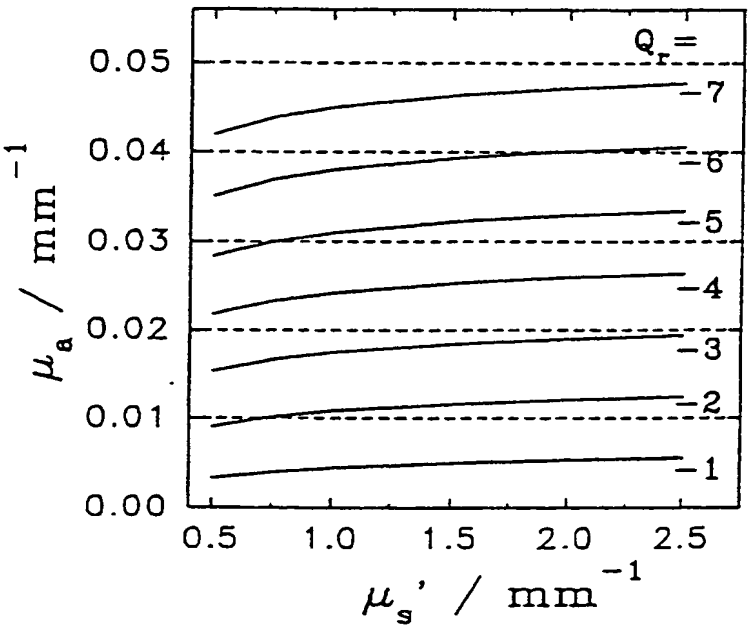

Fig. 4

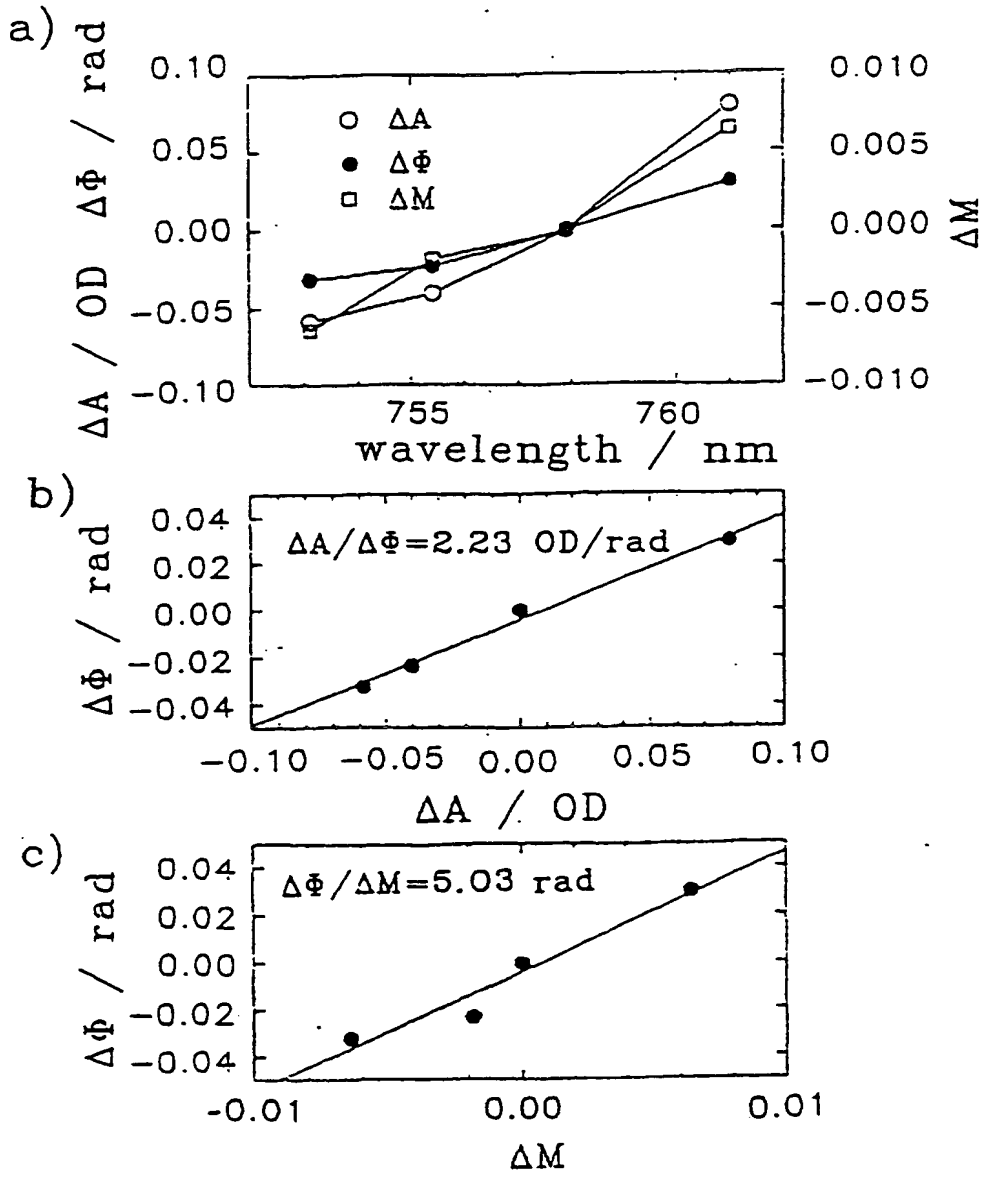
a)
ΔA / OD ΔΦ / rad
ΔM
0.10
0.05
0.00
−0.05
−0.10
0.010
0.005
0.000
−0.005
−0.010
ΔA
ΔΦ
ΔM
755
760
wavelength / nm
b)
ΔΦ / rad
ΔA/ΔΦ=2.23 OD/rad
0.04
0.02
0.00
−0.02
−0.04
−0.10
−0.05
0.00
0.05
0.10
ΔA / OD
c)
ΔΦ / rad
ΔΦ/ΔM=5.03 rad
0.04
0.02
0.00
−0.02
−0.04
-0.01
0.00
0.01
ΔM

Fig. 5

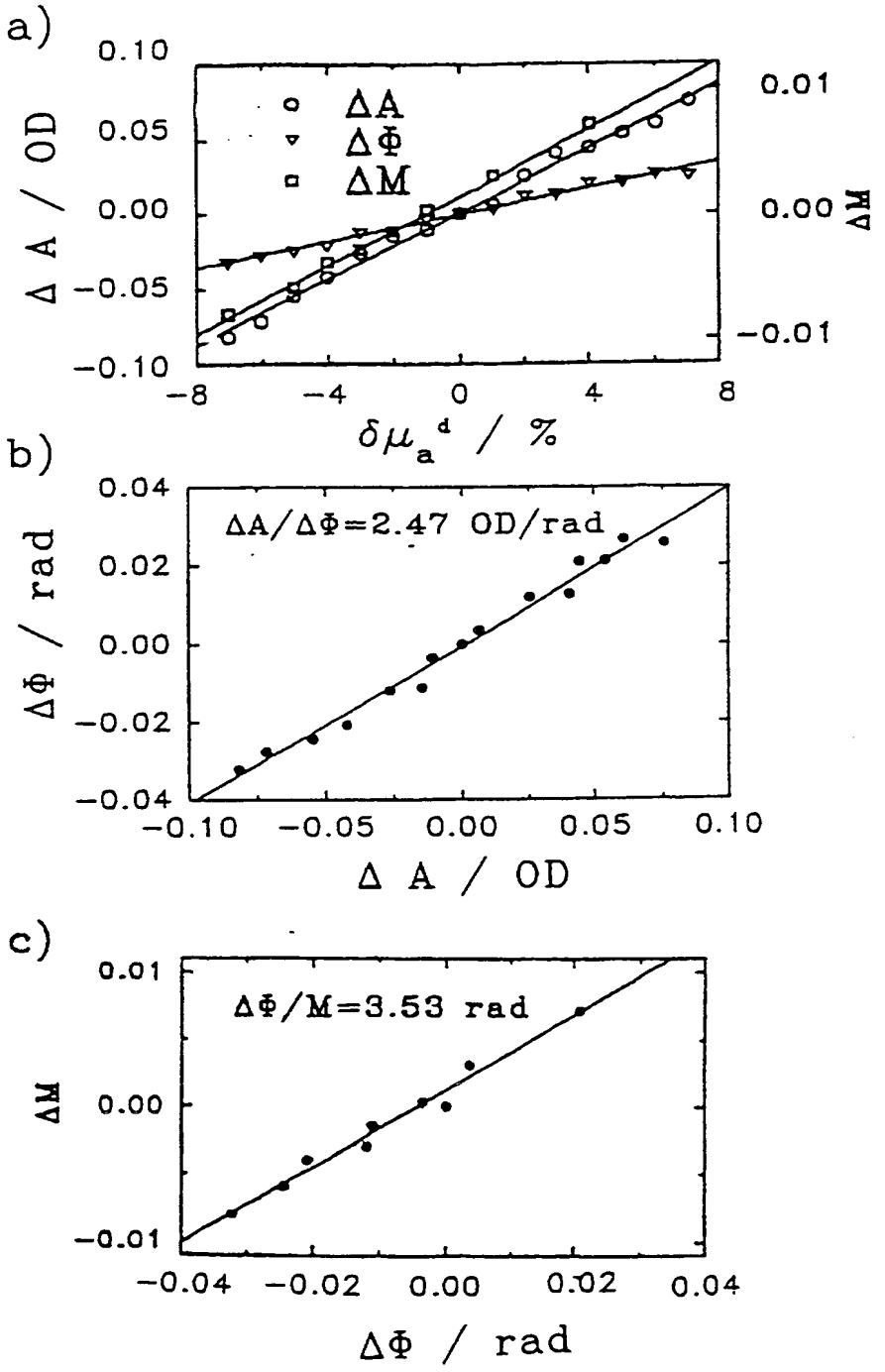
a)
0.10
0.05
0.00
−0.05
−0.10
Δ A / OD
ΔA
ΔΦ
ΔM
0.01
0.00
−0.01
ΔM
−8
−4
0
4
8
δμa d / %
b)
0.04
0.02
0.00
−0.02
−0.04
ΔΦ / rad
ΔA/ΔΦ=2.47 OD/rad
−0.10
−0.05
0.00
0.05
0.10
Δ A / OD
c)
0.01
0.00
−0.01
ΔM
ΔΦ/M=3.53 rad
−0.04
−0.02
0.00
0.02
0.04
ΔΦ / rad

Fig. 6

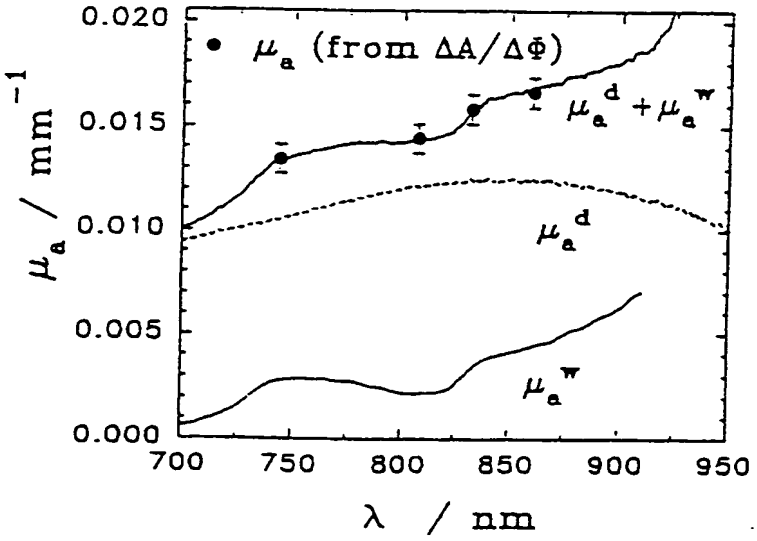
0.020
0.015
0.010
0.005
0.000
μ_a / mm^{-1}
• μ_a (from ΔA/ΔΦ)
$\mu_a^d + \mu_a^w$
μ_a^d
μ_a^w
700
750
800
850
900
950
λ / nm

Fig. 7

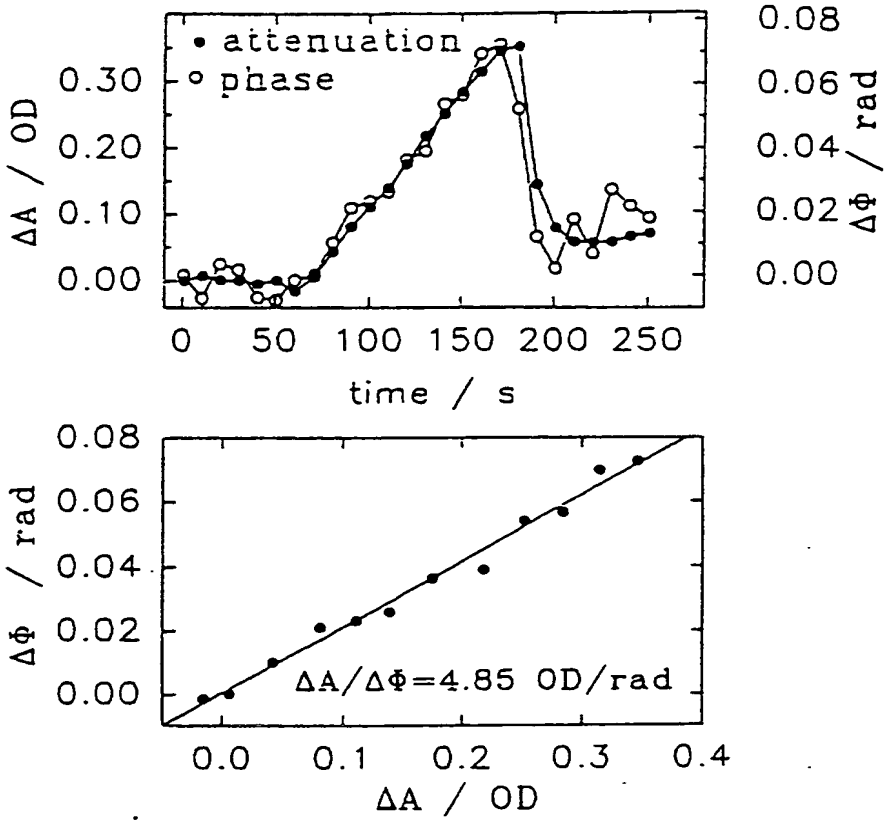
• attenuation
○ phase
ΔA / OD
Δφ / rad
0.30
0.20
0.10
0.00
0.08
0.06
0.04
0.02
0.00
0
50
100
150
200
250
time / s
Δφ / rad
ΔA/Δφ=4.85 OD/rad
0.0
0.1
0.2
0.3
0.4
ΔA / OD

Fig. 8

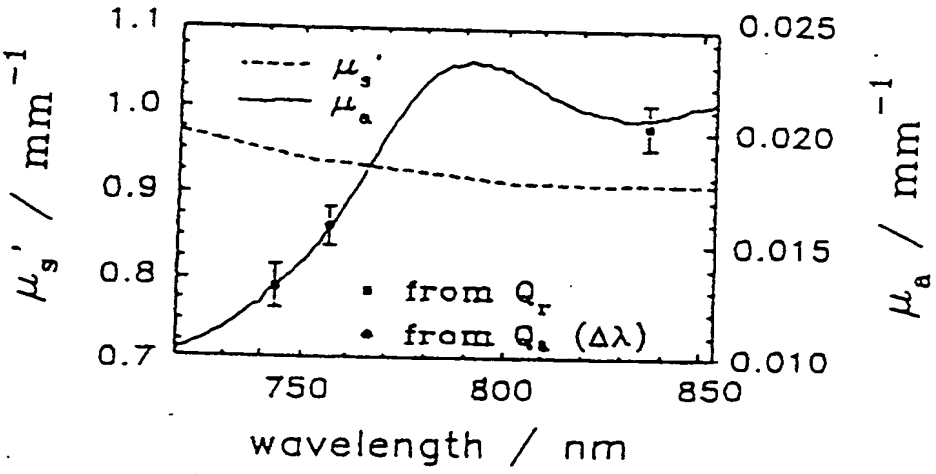
1.1
1.0
0.9
0.8
0.7
0.025
0.020
0.015
0.010
750
800
850
wavelength / nm
μ_s' / mm^{-1}
μ_a / mm^{-1}
μ_s'
μ_a
from Q_r
from Q_a ($\Delta\lambda$)

Fig. 9

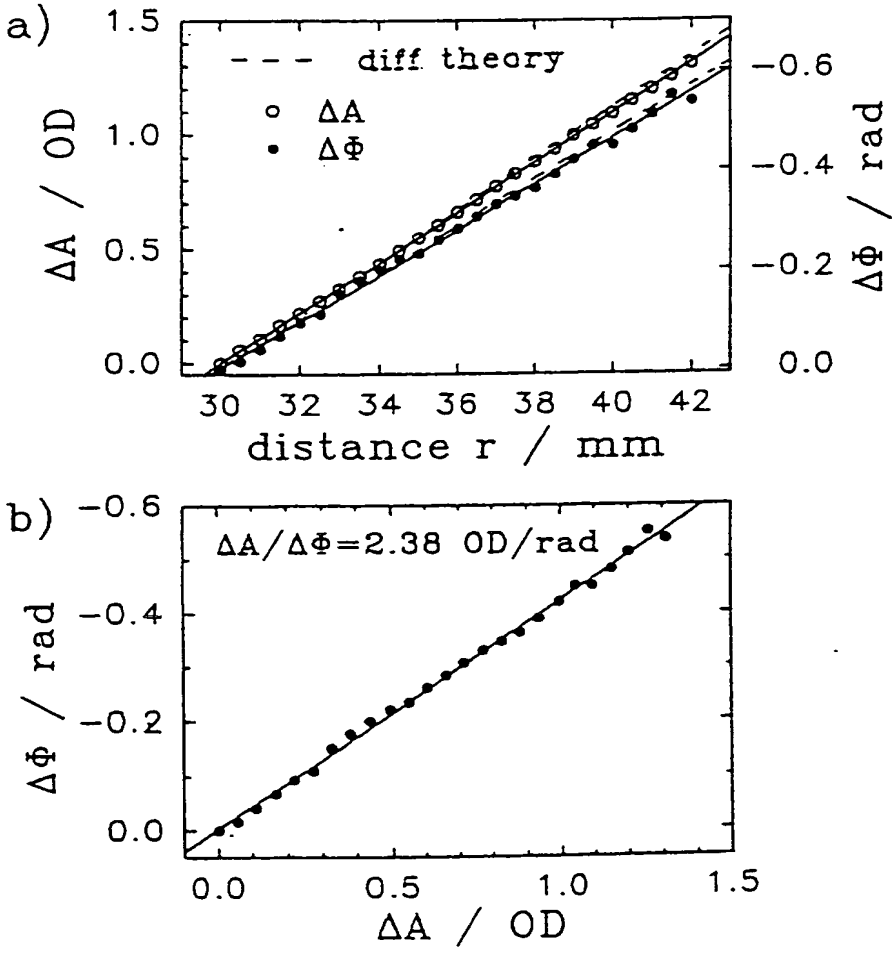
a)
1.5
1.0
0.5
0.0
ΔA / OD
diff. theory
ΔA
ΔΦ
−0.6
−0.4
−0.2
0.0
ΔΦ / rad
30 32 34 36 38 40 42
distance r / mm
b)
−0.6
−0.4
−0.2
0.0
ΔΦ / rad
ΔA/ΔΦ=2.38 OD/rad
0.0 0.5 1.0 1.5
ΔA / OD

Fig. 10

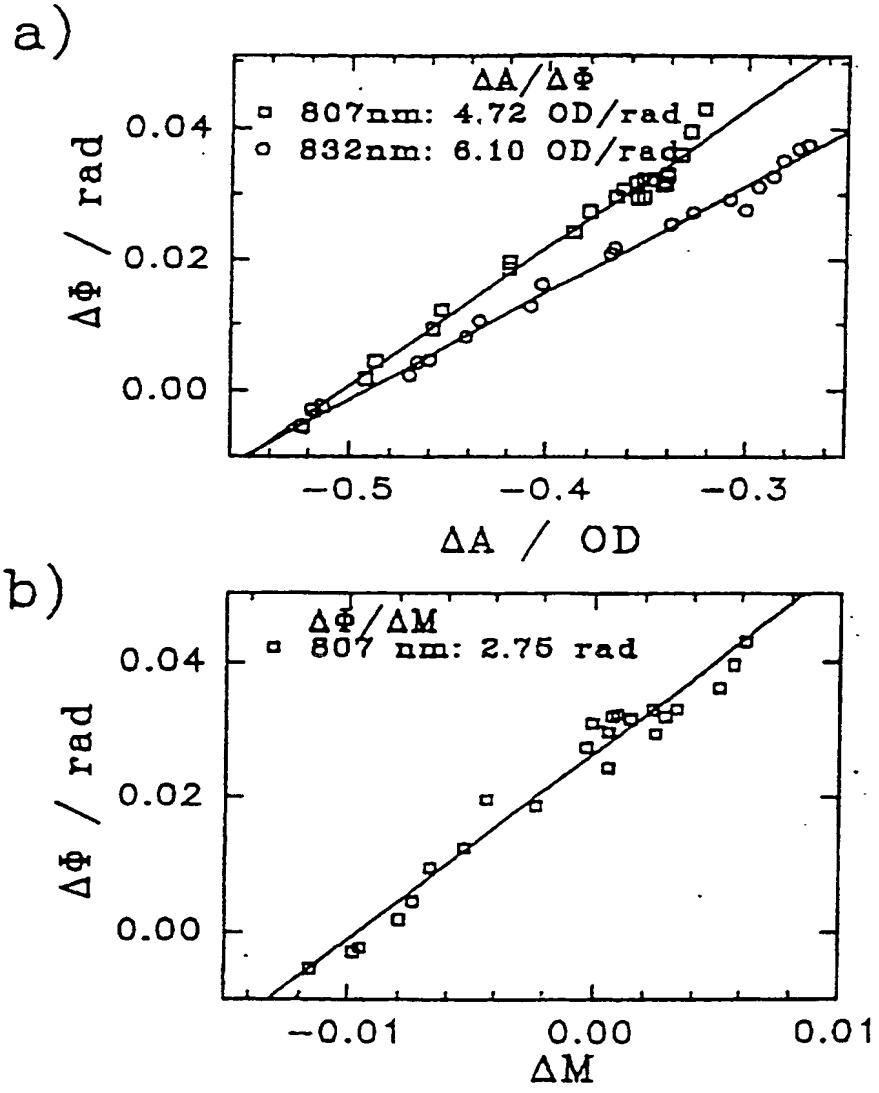
a)
ΔA/ΔΦ
807nm: 4.72 OD/rad
832nm: 6.10 OD/rad
0.04
0.02
0.00
ΔΦ / rad
−0.5
−0.4
−0.3
ΔA / OD
b)
ΔΦ/ΔM
807 nm: 2.75 rad
0.04
0.02
0.00
ΔΦ / rad
−0.01
0.00
0.01
ΔM

Fig. 11

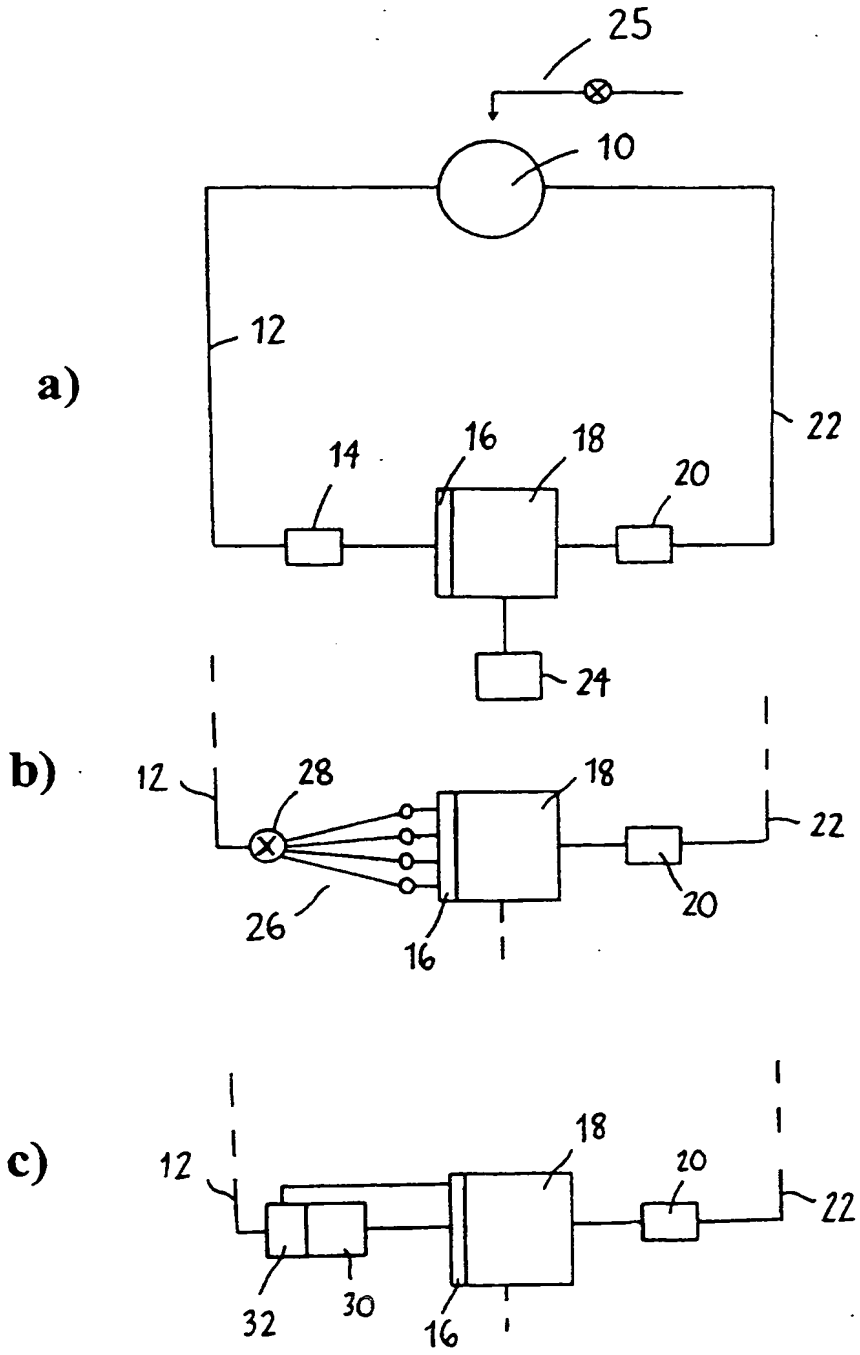

Fig. 12

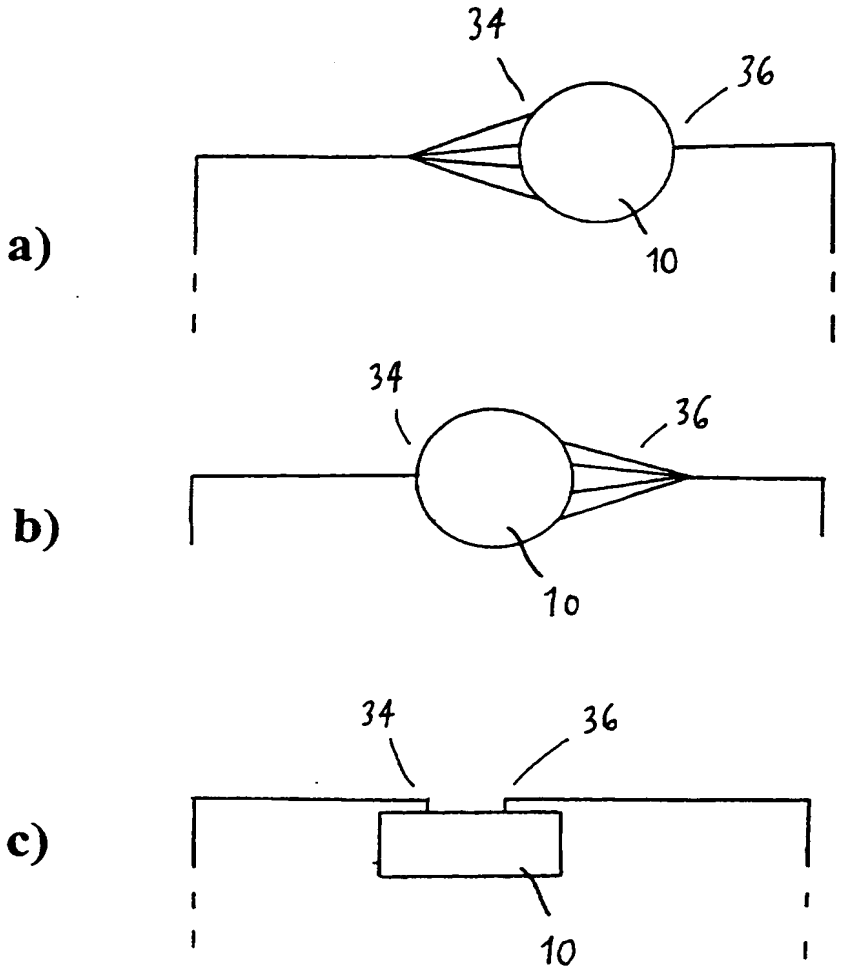

Fig. 13

Determination of absorption coefficients and modified scattering coefficients

This invention relates to the determination of absorption coefficients and modified scattering coefficients in highly scattering media. The invention finds applications in biomedical optics, for example the in vitro or in vivo determination of the concentration of various constituents and chromophores (eg. Hb, HbO_2 or oxygen concentrations) in muscle, brain or other tissue. It also is of use in the determination of absorber concentrations in other turbid media, for example in food and pigment production, or in chemical processes as an aid to manufacturing process control. Furthermore, the invention is of use for the determination of modified scattering coefficients in light scattering media, for the determination of concentrations of (non-absorbing) constituents like electrolytes, glucose, lactate or urea in these media and for the determination of refractive indices.

The analysis of absorption and scattering properties are an important problem in many areas of biomedical optics, in particular for the determination of hemoglobin (Hb), oxyhemoglobin (HbO_2) and cytochrome oxidase concentrations and glucose concentrations in tissue. The different near infrared absorption spectra of these chromophores allow changes in their concentrations to be calculated from changes in the intensity of light diffusely reflected from the tissue surface. However, the absolute concentrations of these chromophores in tissue, ie. the absolute absorption coefficient, cannot easily be inferred.

Different experimental approaches have been suggested for the measurement of absorption coefficients (μ_a) in highly scattering media most of which are based upon the measurement of both the intensity and arrival time (time of flight), or phase of an intensity modulated light source, of the light diffusely exiting from tissue. It has been shown that the absorption and modified

scattering coefficients (μ_a, μ_s') can be inferred from measurements of diffuse intensity and phase for different source detector distances for a fixed modulation frequency. Alternatively, single distance, multiple modulation frequency measurements can be used. For multiple small source detector distances the reflectance measurements are sufficient to derive both μ_a and μ_s'.

In the preferred embodiments of this invention, a different approach for the determination of absorption coefficients is adopted. We have found that small changes in absorption coefficient or other parameters of a system under study (eg the distance between a light-source and a detector) induce changes in diffuse (reflected or transmitted) light intensity and time of flight (or phase Φ) and modulation depth M of an intensity modulated light wave, and that the ratio of these changes is primarily independent of the scattering properties of the medium. This ratio gives a good estimate of the absolute absorption coefficient. This particular approximation is only valid over a certain range of μ_a and μ_s' values. However, this range encompasses the range found in biological tissues in the near infrared. The term "light" used in this specification therefore includes the infrared (particularly the near infrared) as well as the visible spectrum. The modulation depth M is the ratio of the amplitude of the alternating to the steady component of an intensity modulated light wave.

The modified scattering coefficient can readily be inferred from the absorption coefficient and from the intensity, time of flight and or phase or modulation depth measurement.

Thus in one aspect the invention provides a method of determining an absorption coefficient or a modified scattering coefficient of a scattering medium comprising passing light (as herein defined) into the medium, detecting diffuse light emitted from the medium, measuring changes in at least two of the intensity, the phase (or transit time) and the modulation depth of said

light arising from a common cause, and determining the coefficient from said changes.

In another aspect the invention provides a method of determining an absorption coefficient or a modified scattering coefficient of a scattering medium comprising passing light (as herein defined) into the medium, measuring a change in diffuse light emitted from the medium resulting from a small change in the absorption coefficient or in the relative positions of a source and a detector of the light and determining the coefficient from the said change.

The invention also provides apparatus adapted and configured for use in the methods of the invention.

Thus without limitation of the foregoing generality in another aspect the invention provides apparatus for determining an absorption coefficient or a modified scattering coefficient of a scattering medium comprising means for passing light (as herein defined) into the medium, means for detecting diffuse light emitted from the medium, means for causing a change in a parameter of the system formed by the apparatus and the medium, means for measuring resulting changes in at least two of the intensity, the phase (or transit time) thereof and the modulation depth of the emitted light, means for measuring said at least two changes, and means for determining said coefficient therefrom.

In a further aspect the invention provides apparatus for determining an absorption coefficient or a modified scattering coefficient of a scattering medium comprising means for passing light (as herein defined) into the medium, means for inducing a small change in the absorption coefficient or for producing a small change in the relative positions of a source and a detector of the light, means for measuring a resulting change in diffuse light emitted from the medium and means for determining the required coefficient from said resulting change.

Preferably the absorption coefficient is determined from the ratio of the change in the emitted diffuse light intensity and the change in the transit time (phase) thereof, or from the ratio of the change in intensity or phase to the change in modulation depth.

The small change in absorption coefficient may be induced by changing the wavelength of the light passed in to the medium for example by a few nanometres. Alternatively the small change in absorption coefficient may be induced by varying the concentration of a chromophore in the scattering medium.

The method may also include determining a method as claimed in any preceding claim comprising determining the modified scattering coefficient by measuring the intensity or phase or modulation depth of the input emitted from different locations in the medium.

The determining means may determine the absorption coefficient from the ratio of the changes in intensity and transit time.

There may be means for measuring a phase change in the emitted light as the change in transit time.

There may be means for varying the wavelength of the light by a small amount to induce the change in the absorption coefficient.

In one embodiment the means for passing light into the medium comprises a laser diode, the means for varying the wavelength comprising means for varying the operating temperature of the laser.

In another embodiment the means for passing light into the medium comprises a plurality of light sources having closely adjacent wavelengths, the means for varying the wavelength comprising means for switching selectively between said light sources.

In a further embodiment the means for passing light into the medium comprises a source of white light, the means for varying the wavelength comprising means for selecting individually a plurality of closely adjacent wavelengths from the white light.

The light source and the detector may be a moveable apparatus as claimed in claim 11 wherein the light source and/or the detector is moveable and/or there are a plurality of light sources and/or detector at spaced apart locations.

Other features of the invention are as set out in the claims.

The following is a more particular but non-limiting description of the invention, including some examples, and refers to the accompanying drawings, wherein:

Figure 1 - shows Q_a and V_a as a function of μ_a.

Figure 2 - shows lines of constant Q_a as a function of μ_a and μ_s' calculated for ν_M = 200MHz, n = 1.33 and r = 30mm.

Figure 3 - shows $Q_r = (\partial A/\partial r)/(\partial \Phi/\partial r)$ and $V_r = \partial \Phi/\partial r)/(\partial M/\partial r)$ as a function of μ_a calculated from equations 8 and 9 for r = 35mm, μ_s'= 0.75, 1.0, 1.25 and 1.50mm^{-1} and n = 1.56.

Figure 4 - shows lines of constant Q_r as a function of μ_a and μ_s'calculated for ν_M = 200MHz, n = 1.56 and r = 35mm.

Figure 5 - a) shows experimentally measured changes in attenuation ΔA, phase $\Delta\Phi$ and modulation depth for variations in wavelength. In b) the correlation ΔA, phase $\Delta\Phi$ is shown. In c) the correlation of $\Delta\Phi$ and ΔM is shown.

Figure 6 - (a) shows experimentally measured changes in attenuation ΔA, phase $\Delta\Phi$, and modulation depth ΔM with changes in the absorption coefficient μ_a. In b) the correlation $\Delta\Phi$, and ΔA is shown and in c) the correlation of $\Delta\Phi$ and ΔM.

Figure 7 - shows absorption coefficient $\mu_a = \mu_a^w + \mu_a^d$ of the liquid phantom, where μ_a^w is the water absorption and μ_a^d is the dye absorption for a concentration of $c_d = 1.40 \times 10^{-5}$ v/v. The dots are the experimental absorption coefficients derived from experiment for the four laser wavelengths.

Figure 8 - (a) shows the change of attenuation ΔA and phase $\Delta\Phi$ during a cuff occlusion of the forearm of a volunteer, for optode distance r = 40mm, λ = 740nm. Figure 8 (b) shows the correlation between ΔA and $\Delta\Phi$ for the data shown in (a) for 50s < t < 170s. The slope of a first order regression is $\Delta A/\Delta\Phi$ = 4.67 OD/rad.

Figure 9 - shows the absorption coefficient μ_a (solid line) and modified scattering coefficient μ_s' (dashed line) of a solid phantom (errors ± 1% and ± 2%, respectively). The absorption coefficients derived from $Q_a(\Delta\lambda)$ (see Figure 5, filled dot) and Q_r (see Figure 10, filled squares) are shown. The error bars represent the variations by assuming modified scattering coefficients between $0.75mm^{-1} < \mu_s' < 2mm^{-1}$.

Figure 10 - (a) shows attenuation changes (ΔA) and phase changes ($\Delta\Phi$) as a function of source-to-detector distance r measured on a solid phantom ($\mu_a = 0.0135mm^{-1}$, $\mu_s' = 0.94mm^{-1}$, n = 1.56 for λ = 744nm, compare with Figure 9). The solid lines are the first order regression lines through the data and the dashed lines were calculated by diffusion theory (equation 8 and 9) and (b) shows the correlation of ΔA and $\Delta\Phi$ for the data shown in (a). The first order regression has a slope $\Delta A/\Delta\Phi$ = 2.38 OD/rad. The absorption coefficient μ_a derived from this slope is shown in Figure 9.

Figure 11 - shows experimentally determined correlations between ΔA and $\Delta\Phi$, and between $\Delta\Phi$ and ΔM, measured on the head of a fetus. The data was collected during one contraction.

Figures 12 and 13 - show various forms of apparatus according to the invention.

The transport of light in scattering media may be analyzed by diffusion theory to describe light intensity, time of flight and phase and modulation depth in terms of the modified scattering coefficient μ_s', the absorption coefficient μ_a and the refractive index n of the medium. For a "pencil beam" light source on a semi-infinite half space, the reflectance R and the mean transit time ("time of flight") <t> detected at a distance r from the source can be written as

$$R(\rho) = z_0 \cdot \left(\frac{1}{\rho} + \mu_{eff}\right) \cdot \frac{\exp(-\mu_{eff} \cdot \rho)}{2\pi \cdot \rho^2} \qquad (1)$$

and

[184e

$$\langle t \rangle(\rho) = \frac{\rho^2}{2c \cdot (D + \rho \cdot \sqrt{\mu_a \cdot D})} \qquad (2)$$

respectively. In equation (1) and (2) $\rho=(r^2+z_0^2)^{1/2}$, $z_0=1/\mu_s'$, $c=c_0/n$ is the velocity of light in the medium (speed of light in vacuum c_0), $\mu_{eff}=[3\cdot\mu_a\ (\mu_a+\mu_s')]^{1/2}$ is the effective attenuation coefficient and $D=\frac{1}{3(\mu_a+\mu_s')}$ is the diffusion coefficient.

Here the changes of the reflectance and the mean time with respect to changes in μ_a are considered whilst the scattering properties are assumed to be constant. Any changes in the absorption coefficient ($\Delta\mu_a$) changes the reflectance from R_0 to $R=R_0+\Delta R(\Delta\mu_a)$ and the mean time from $\langle t\rangle_0$ to $\langle t\rangle = \langle t\rangle_0 + \Delta\langle t\rangle$. The derivative of the attenuation or change in intensity A, define by $A=\log(R_0/R)$, and <t> with respect to μ_a are

$$\frac{\partial A}{\partial \mu_a} = \frac{3}{2 \cdot \ln 10} \cdot \frac{\rho}{1/\rho + \mu_{eff}} \cdot (2\mu_a + \mu_s') \qquad (3)$$

and

$$\frac{\partial \langle t \rangle}{\partial \mu_a} = \frac{-3}{2 \cdot (1/\rho + \mu_{eff})^2 \cdot c} \cdot \left(\frac{\rho}{2} \cdot \frac{\mu_s'}{\sqrt{\mu_a D}} - 1\right) \qquad (4)$$

For the diffusion approximation to apply, $\mu_a << \mu_s'$ and therefore $\mu_{eff} \approx (3\mu_a\mu_s')^{1/2}$ and $D \approx 1/(3\mu_s')$. Using these approximations and dividing equation (3) by equation (4) gives

$$\frac{\partial A}{\partial \mu_a} \Big/ \frac{\partial \langle t \rangle}{\partial \mu_a} = \frac{-(1+\rho \cdot \mu_{eff}) \cdot c}{\ln 10 \cdot \left(\frac{\rho \cdot \mu_{eff}}{2} - \frac{\mu_a}{\mu_s'}\right)} \cdot \mu_a \qquad (5)$$

For the optical properties and source detector distances here contemplated, $\rho \cdot \mu_{eff}/2 >> \mu_a/\mu_s'$ and therefore

$$\frac{\partial A}{\partial \mu_a} \Big/ \frac{\partial \langle t \rangle}{\partial \mu_a} = \frac{-2 \cdot (1/\mu_{eff} + \rho) \cdot c}{\ln 10 \cdot \rho} \cdot \mu_a \qquad (6)$$

For $\rho > 1/\mu_{eff}$, this expression is in good approximation independent of μ_s', i.e. it is a linear function of μ_a only.

When a frequency domain spectrometer (FDS) or intensity modulated optical spectrometer (IMOS) is used to measure chromophore concentrations, the phase Φ of a light wave, intensity modulated at the frequency ν_M, is measured rather than the mean time $\langle t \rangle$. Φ and $\langle t \rangle$ are approximately coupled by a simple linear relationship at frequencies less than approximately 200 MHz:

$$\Phi = -2\pi \cdot \nu_M \cdot \langle t \rangle \tag{7}$$

The derivative of attenuation and <t> with respect to the source detector distance r is:

$$\frac{\partial A}{\partial r} = \frac{1}{\rho^2 \cdot (1/\rho + \mu_{eff})} + \frac{1}{\ln 10} \cdot (2/\rho + \mu_{eff}) \tag{8}$$

and

$$\frac{\partial \langle t \rangle}{\partial r} = \frac{3\rho \cdot (2 + \rho \cdot \mu_{eff})}{2c \cdot (1 + \rho \cdot \mu_{eff})^2} \cdot (\mu_s' + \mu_a) \tag{9}$$

Alternatively, when a frequency domain spectrometer is used, the phase Φ and the modulation depth M, ie. the ratio of the ac to the dc component of the modulated light wave, can be written as:

$$\Phi = \psi_r - \tan^{-1}\left(\frac{\psi_r}{1 + \psi_i}\right) \tag{10}$$

and

$$M = \frac{\sqrt{1 + \psi_0^2 + 2\psi_i}}{1 + \psi_-} \cdot \exp(\psi_- - \psi_i) \tag{11}$$

where

$$\psi_0 = \sqrt{3(\mu_a + \mu_s')} \cdot \sqrt{\mu_a^2 c^2 + (2\pi\nu_M)^2} \cdot c^{-1} \cdot \rho \tag{12}$$

$$\psi_r = -\psi_0 \cdot \sin(\theta/2) \quad (13)$$

$$\psi_i = \psi_0 \cdot \cos(\theta/2) \quad (14)$$

$$\theta = \tan^{-1}\left(\frac{2\pi\nu_M}{\mu_a c}\right) \quad (15)$$

and

$$\psi_\infty = \psi_0(\nu_M=0) = \psi_i(\nu_M=0) = \sqrt{3\mu_a(\mu_a+\mu_s')} \cdot \rho \quad (16)$$

The equations given above are valid for a homogeneous semi-infinite halfspace. For other geometries, the equations have to be modified accordingly. The method described in this preferred embodiment of the present invention, however, is equally able to derive μ_a from these modified equations.

In Fig.1a, $Q_a = (\partial A/\partial\mu_a)/(\partial\Phi/\partial\mu_a)$, the ratio of attenuation change over phase change is shown as a function of the absorption coefficient μ_a. The curves in Fig. 1a were calculated from the frequency equation for modified scattering coefficients of μ_a = 1.0 mm^{-1}, 1.25 mm^{-1} and 1.50 mm^{-1}, a source - detector distance r=30 mm, a modulation frequency ν_M =200MHz and a refractive index of n=1.33. It can be seen from Fig. 1a that a good first order approximation is that Q_a varies linearly with μ_a. It can also be seen that the influence of μ_s' on Q_a is small. Therefore, under the condition of a fixed geometry, constant scattering properties and pure absorption changes, Q_a is primarily dependent on μ_a only. Consequently, measured attenuation and phase changes yield a good estimate of the absolute (mean) absorption coefficient. The horizontal lines in Figure 1a give the measured values of Q_a for four different

wavelengths of the spectrometer in the experiment described below.

To further estimate the dependence of Q_a on μ_s', lines of constant Q_a are shown in Fig. 2 as a function of μ_a and μ_s'. It demonstrates that for a change from μ_s' =0.5 mm^{-1}, to μ_s' = 1.5 mm^{-1}, ie. about the range of scattering coefficients expected for tissue, the corresponding absorption coefficient varies by about 10% only. Hence, the exact knowledge of the scattering properties is not required for the prediction of μ_a to this degree of accuracy. For a given tissue type μ_s' is unlikely to vary by as much as 0.5 - 1.5 mm^{-1}, leading to a more accurate μ_a estimation. However, the method suggested here assumes that the scattering properties of the medium do not change.

Figure 1b shows the ratio $V_a = (\partial\Phi/\partial\mu_a)/(\partial M/\partial\mu_a)$, the ratio of the phase changes over changes in modulation depth, as a function of absorption coefficient. The same optical properties of the medium were assumed as in figure 1a. The influence of the different values of μ_s' on V_a is negligible. To a good approximation, V_a is a linear function of μ_a. Therefore, figure 1b allows μ_a to be derived from measured values of V_a. Equivalent considerations are valid for the ratio of changes in attenuation and changes in modulation depth.

Equations 1 to 16 assume a matched boundary between medium and surrounding. On applying the physically more correct mismatched boundary condition for the calculation of reflectance, mean time and modulation depth the values for Q_a and V_a differ only slightly from the data in Fig. 1.

The quotient $Q_r = (\partial A/\partial r)/(\partial\Phi/\partial r)$ calculated from equation 8 and 9 is shown in figure 3a as a function of μ_a. A refractive index of n =1.56 and a source detector distance of r= 35 mm was assumed. Similar to figure 1, the influence of the modified scattering coefficient on Q_r is small. Consequently, measuring the ratio of changes in attenuation and phase with respect to r

gives an estimate of μ_a. The influence of μ_s' on the estimated values of μ_a, for constant values of Q_r, is shown in figure 4. The uncertainties in μ_a, due to variations in μ_s', are of the same magnitude as for Q_a (compare with figures 1, 2).

The ratio $V_r = (\partial\Phi/\partial r)/(\partial M/\partial r)$ is shown in figure 3b. Similar to Q_r, the influence of μ_s' on V_r is small, allowing μ_a to be derived from a measured value of $\Delta\Phi/\Delta M$.

Thus, if an object is probed with light (as defined), the concentrations of the constituent substances within the body can be estimated from measurements of the attenuation and pathlength (time of flight) or from measurements of changes in pathlength and modulation depth or changes in attenuation and modulation depth. There are two technologies that may be used to measure both the attenuation and pathlength of light through an object. As the two methodologies, time domain or frequency domain, are distinct each method will be described separately.

Time Domain Measurement

The attenuation and pathlength of light through an object can be measured most accurately in the time domain by using a picosecond laser and a light detection device such as a streak camera. The laser is used to deliver an ultrashort light pulse to the object and the light detection device is then used to measure how the shape of this pulse is changed by its interaction with the object (i.e. the detection device measures the impulse response).

If the measured impulse response is a function $g(t)$, with a mean $\langle t \rangle$ given by,

$$\langle t \rangle = \frac{\int_{-\infty}^{\infty} g(t)\, t\, dt}{\int_{-\infty}^{\infty} g(t)\, dt} \qquad (17)$$

the pathlength (or mean time of flight) can then be calculated from the expression

$$\langle d \rangle = \langle t \rangle \frac{c_0}{n} \qquad (18)$$

where c_o is the velocity of light in vacuum and n is the mean refractive index of the object being probed.

Systems of the above type are large and expensive and this is likely to preclude their use in all but the laboratory setting, or as fixed equipment in manufacturing or processing plant.

Suitable light sources for use in such systems are ion laser pumped dye lasers and ion laser pumped solid state lasers. Suitable detectors are streak cameras, microchannel plate photomultiplier tubes and time resolved single photon counting systems.

Alternatively, because only the mean pathlength or transit time need be investigated and not the complete impulse response of the object being probed, it is possible to use simpler instrumentation, with a poorer time resolution. This alternative method consists of probing the object with a broad pulse.

Frequency Domain Measurement

To measure the attenuation and pathlength of light through an object, via the frequency domain, a modified intensity modulated optical spectrometer (IMOS) is used. With an IMOS the intensity of the light is sinusoidally modulated at high frequencies (i.e. typically > 1 MHz). A phase sensitive detector then determines the difference between the phase of the optical waveform entering the object and the phase of the optical waveform leaving the object. As the measured phase difference is a linear function of the pathlength, the pathlength can be easily determined.

Thus, using either an instrument for time domain measurements or for frequency domain measurements to detect intensity and time of flight (or phase) and modulation depth changes, it is possible to determine the absorption coefficient and the modified scattering coefficient.

One approach to obtain Q_a is to induce small changes in absorption coefficient by tuning the wavelength λ ie. to scan over the absorption spectrum of the scattering medium. It is necessary that the scattering coefficient does not change materially for these wavelengths.

To demonstrate this technique, a solid, light scattering phantom with well characterised optical properties (for λ = 758 nm; μ_a = 0.0160 mm; μ_s' = 0.934 mm; n=1.56; $\partial_{\mu a}$ = +1.5% per nm; $\partial\mu_s'$ = -0.05% per nm) was used. A temperature tuneable diode laser was employed to change the wavelength between λ = 753 nm and λ = 761 nm (FWHM = 2 nm). The light reflected from the phantom was detected at a distance r = 30 mm from the light delivery fibre and attenuation and phase changes were corrected for instabilities in the diode laser output by reference measurements at a distance r = 7mm.

Figure 5a shows the measured changes in attenuation, phase and modulation depth for this wavelength range. The first order

regression of the correlation plots gives slopes of Q_a = 2.23 OD/rad (figure 5b) and V_a = 5.03 rad (figure 5c). By analysing these values according to equations given above, an absorption coefficient of μ_a = 0.0161 mm^{-1} for 0.75 mm^{-1} < μ_s' <2.0 mm^{-1} was calculated from Q_a and μ_a = 0.0163 mm^{-1} from V_a. This is in excellent agreement with the true value of μ_a.

The wavelengths have to be adjusted to the absorption spectrum of the chromophores. The absorption coefficients of hemoglobin and oxyhemoglobin for example change by up to $\partial_{\mu a}$ = ±2% per $\Delta\lambda$=1mm, i.e. a variation of the wavelength by a few nm is sufficient to induce large enough absorption changes.

Thus by modifying the IMOS to permit tuning of the wavelength of the light source over a narrow range eg. a few nanometres, for example (between 5 and 20 nm) the resulting change in attenuation ΔA, phase $\Delta\Phi$ and modulation depth ΔM can be measured, enabling the absolute absorption coefficient to be determined. Because μ_a is determined from ΔA, $\Delta\Phi$ and modulation depth ΔM for the same $\Delta\lambda$, the exact value of $\Delta\lambda$ is not critical.

The IMOS light source may for example be a modified laser diode, a modulated light emitting diode or a lamp whose output is controllable with the necessary speed and precision. Modulation may be by any single or multifrequency sinusoidally based scheme. Suitable detectors for the IMOS are photomultiplier tubes, photodiodes and CCD (charge coupled device) detectors.

The wavelength tuning capability may be achieved in a number of ways, for example as already stated by adjusting the temperature of the light source, or by adjusting the current supply, or by a tunable absorbance filter. Alternatively, a white light source may be used with a Pockel cell and other wavelength selective device (eg. a prism or grating) as a number of discrete selectable light sources with closely spaced wavelengths (e.g. multiple LEDs) may be employed.

In an experiment to determine an absorption coefficient by concentration adjustment, a frequency domain spectrometer was used incorporating four different laser diodes (λ=744 nm, 807 nm, 832nm, 860 nm) that were intensity modulated with a frequency of ν_M=200 MHz. Phase sensitive amplifiers detected the phase shift of the multiple scattered light. Optical fibres were used to transport the light between light source, and the scattering medium and between the scattering medium and detector.

Scattering phantoms of known absorption and modified scattering coefficient (μ_a and μ_s', respectively) were employed to demonstrate the method. The phantoms consisted of spherical polystyrene particles suspended in water serving as light scattering centres. Mie theory was used to derive the modified scattering coefficient μ_s' for these spheres (diameters between 0.6 µm and 2.5 µm). The absorption coefficient of the phantom (μ_a) was that of water (μ_a^w) and of a dye (μ_a^d) (S109564, ICI, Manchester, UK) added in known quantities: $\mu_a = \mu_a^w + \mu_a^d$. The spectrum of $\mu_a^w + \mu_a^d$ for a dye concentration of $c_d = 1.40 \times 10^{-5}$ v/v is shown in Fig.7. The ends of the light delivering and detecting fibres of the frequency domain spectrometer were submerged approximately 2 mm into the phantom of a volume V = 100 mm x 80 mm x 60 mm.

The absorption coefficient μ_a of the phantom was changed by varying the concentration of the dye c_d in 14 steps of 1.44 % each (corresponding to $\Delta\mu_a = 1.56 \times 10^{-4}$ mm^{-1} at λ = 744nm). The concentration of the scattering microspheres c_s was 1 % v/v and held constant. The resulting optical properties of the phantom are listed in table 1 for the different laser wavelengths. The wavelength dependence of μ_s' is insignificant while μ_a varies by about 30 %. The values of μ_a given in table 1 are for a dye concentration of $c_d = 1.40 \cdot 10^{-5}$ v/v.

	phantom properties		experimental	
λ / nm	μ_s' / mm^{-1}	$\mu_{a,}$ / mm^{-1}	Q_a / OD/rad	μ_a / mm^{-1}
744	1.22	0.0133	2.47	0.0135
807	1.18	0.0142	2.66	0.0144
832	1.16	0.0157	2.93	0.0158
860	1.13	0.0169	3.08	0.0166

Optical properties of the phantom for four different wavelengths λ. The value of μ_s' was derived from Mie theory. μ_a consists of the dye absorption μ_a^d and the water absorption μ_a^w. The last two columns give the measured ratio of the attenuation and phase change ($\Delta A/\Delta\Phi$) and the corresponding absorption coefficient derived from Fig. 1.

The changes in intensity phase and modulation depth as a function of changes in the absorption coefficient were recorded using the frequency domain spectrometer. This is shown in Fig. 6a for λ = 744 nm. On plotting ΔA against ΔΦ (see Fig. 6b) it can be seen that both are strongly correlated. A first order regression gives a slope of $\Delta A/\Delta\Phi$ = 2.47 OD/rad. By using this measured value of $Q_a = \Delta A/\Delta\Phi$ and the known modified scattering coefficient, Fig. 1a allows the absorption coefficient μ_a to be read. The experimental values of Q_a are listed in table 1 and shown in Fig. 1a for all four wavelengths. The corresponding absorption coefficients were read from Fig. 1a and are plotted in the absorption spectrum of Fig. 7. They agree with the expected values to within a few percent (compare table 1). The correlation between ΔM and ΔΦ is shown in figure 6c. A first order regression gives a slope of $\Delta\Phi/\Delta M$ = 3.53 rad. Using this value allows μ_a to be read from figure 1b to be 0.0135 mm^{-1}. This is in agreement with the true μ_a value as well.

In a second experiment the method was used to determine an absorption coefficient in vivo and thereby demonstrate the change of blood flow during venous occlusion.

Fig. 8a shows attenuation and phase changes for a wavelength

λ = 740 mm during a cuff occlusion of the forearm of a healthy volunteer. The optode spacing was r=40 mm and the modulation frequency of the frequency domain spectrometer ν_M=200 MHz. The pressure in the cuff was increased to about 200 mm Hg at t=60 s and released at t=180 s. Both the attenuation and the phase difference increase during the occlusion, indicating an increase in the absorption coefficient due to a change in the oxygenation of the blood. The correlation between attenuation and phase change for times between 50 s and 170 s (see Fig. 8b) gives a slope $\Delta A/\Delta\Phi$ = 4.85 OD/rad. Assuming a refractive index of the tissue of n = 1.4 equations 3, 4 and 7 give values for the absorption coefficient of μ_a = 0.026 mm^{-1} (for μ_s' = 0.5 mm^{-1}) and μ_a = 0.028 mm^{-1} (for μ_s' = 1.0 mm^{-1}).

In a further experiment the attenuation and phase changes were measured on the head of a fetus during labour. Contractions change the blood flow and volume in the baby's head, i.e. induce changes in absorption coefficient. Figures 11a and b show the correlation of attenuation and phase changes and the correlation of phase and modulation depth changes measured during one contraction of about 1.5 minutes duration for two wavelengths (λ_1 = 807 nm and λ_2 = 832 nm). The measured slope $\Delta A/\Delta\Phi$ (λ_1) = 4.72 OD/rad corresponds to μ_a (λ_1) = 0.026 mm^{-1} and the slope $\Delta A/\Delta\Phi$ (λ_2) = 6.1 OD/rad corresponds to μ_a (λ_2) = 0.033 mm^{-1}. Using the absorption coefficients of pure hemoglobin and oxyhemoglobin at both wavelengths, the oxygen saturation of the blood of the tissue probed by the light can be calculated to be 77%. The measured slope of phase and modulation depth changes $\Delta\Phi/\Delta M$ (λ_1) = 2.75 rad (see figure 11b) corresponds to μ_a (λ_1) = 0.012 mm^{-1}. This absorption value is different from that derived from $\Delta A/\Delta\Phi$. That is due to the fact that attenuation and modulation depth probe different volumes of the tissue. While attenuation measurements are more susceptible to changes in the volume close to the light source detector, ie. to the surface of the medium, the phase and modulation depth probe predominantly volume deep within the medium. $\Delta\Phi/\Delta M$ is therefore more likely to give the absorption coefficient (and oxygen saturation) of the deeper

layers of the brain. Contrary, $\Delta A/\Delta \Phi$ derives the absorption coefficient of the outer tissue layers.

Experiments on phantoms were undertaken to derive μ_a from measurements with varying source detector separations. The attenuation and phase changes were measured as a function of the source detector distance for the solid scattering phantom (see Figure 10a). The optical properties of the phantom were n = 1.56, μ_a = 0.0134 mm^{-1} and μ_s' = 0.094 mm^{-1} for λ = 744 nm. In figure 10b, the correlation of ΔA and $\Delta \Phi$ = 2.38 OD/rad. Analysis of this slope according to equation 8 and 9 (compare figure 3 and 4) yields an absorption coefficient 0.0135 (± 0.0010) mm^{-1} for assumed modified scattering coefficients between 0.75 mm^{-1} < μ_s' < 2 mm^{-1}. This is in excellent agreement with the true value of 0.0134 mm^{-1}.

Using the estimated value of μ_a, together with the measured ΔA, allows the modified scattering coefficient to be calculated from equation 1. The slope of the first order regression, $\Delta A/\Delta r$, in figure 10a is 0.109 OD/mm (λ = 744 nm) giving μ_s'= 0.900 (± 0.0065) mm^{-1} for μ_a = 0.0135 (±0.001) mm^{-1}. These values are in agreement, to within the error limits, with the true μ_s'. Equivalently, the slope of the phase $\Delta \Phi/\Delta r$ = -0.0460 rad/mm. Using this value together with the estimated μ_a and equation 2 a modified scattering coefficient of μ_s'= 0.902 (±0.065) mm^{-1} is obtained.

Figures 12A, 12B, and 12C show diagrammatically various forms of apparatus of the invention. The apparatuses of Figures 12B and 12C are the same as that of Figure 12A except as illustrated.

In Figure 12A, a sample 10 is supplied with light as hereinbefore described via an optical fibre 12 from a source 14. The source is driven by control circuitry 16 of a spectrometer 18 so as to have known amplitude and phase; the circuitry 16 controls the operating temperature or driving current to adjust the wavelength of the light over a small range. A detector 20 receives diffused

light from the sample 10 via optical fibre 22, enabling the spectrometer and computing equipment 24 connected thereto to determine μ_a as already described.

Shown diagrammatically at 25 are means such as a controllable supply of solvent for adjusting the concentration of the sample as an alternative means of varying the absorption coefficient μ_a.

In Figure 12B the light source 14 is replaced by four separate sources 26, connected via a coupler 28 to the optical fibre 12. The control circuitry 16 switches selectively between them to vary the wavelength of the light supplied to the sample.

In Figure 12C, the light source 14 is replaced by a white light source 30, in connection with a Pockel cell, prism or grating 32 controlled from the control circuitry 16 to provide monochromatic light of known and controllable wavelength.

Figure 13 shows variations in the source/detector configuration when a change in the relative positions thereof is employed to generate the changes in A, Φ or M. Except as now described the apparatus is as in figure 12A except that the wavelength of the light source is fixed.

In figure 13A, the sample 10 is illuminated by one of four selectively switchable light sources 34, the diffuse light being received in transmittance (through the sample) by detector 36. Selecting different ones of the light source changes by a small account the distance between the light source and the detector. It is not necessary to measure the exact change in distance; it is sufficient that it is the common cause of a change in A, Φ and M.

The apparatus of figure 13B is similar to that of figure 13A except that there is a single light source 34 and a plurality of suitable detectors 36. Similar changes in source-detector distance are achieved.

In figure 13C there is a single light source 34 and a single detector 36 which is arranged to receive diffuse light reflected out of the same surface of the sample 10 as it entered. The source-detector distance is adjusted by moving one or both of the source and detector. Alternatively several switchable sources or several switchable detectors can be provided as in figures 13A and 13 B.

The main features and advantages of the specifically-described embodiments of the invention are:

A single source detector distance is sufficient to determine μ_a when the changes in ΔA, $\Delta \Phi$ and ΔM are induced by absorption changes are used. The absolute change in distance does not need to be known to determine μ_a when the changes in ΔA, $\Delta \Phi$ and ΔM are induced by variations in the source detector distance.
A single modulation frequency is sufficient.
Changes in intensity, phase and modulation depth are measured rather than absolute values.
Therefore, the technology needed is simpler than that for other methods.

Each feature disclosed in this specification (which term includes the claims) and/or shown in the drawings may be incorporated in the invention independently of other disclosed and/or illustrated features.

The following abstract was filed with the application and is repeated here as part of the specification: a method of determining the absolute absorption coefficient (chromophore concentration) and the modified scattering coefficient in highly scattering media, comprising measuring the intensity and phase and modulation depth changes that are induced by small absorption coefficient changes or changes in source detector distance.

CLAIMS

1. A method of determining an absorption coefficient or a modified scattering coefficient of a scattering medium comprising passing light (as herein defined) into the medium, detecting diffuse light emitted from the medium, measuring changes in at least two of the intensity, the phase (or transit time) and the modulation depth of said light arising from a common cause, and determining the coefficient from said changes.

2. A method as claimed in claim 1 wherein the common cause is a small natural or induced change in the absorption coefficient or a small change in the relative positions of a light source to a detector thereof.

3. A method of determining an absorption coefficient or a modified scattering coefficient of a scattering medium comprising passing light (as herein defined) into the medium, measuring a change in diffuse light emitted from the medium resulting from a small change in the absorption coefficient or in the relative positions of a source and a detector of the light, and determining the coefficient from the said change.

4. A method as claimed in any preceding claim wherein the absorption coefficient is determined from a ratio of two said changes.

5. A method as claimed in claim 1 where the change in the transit time is measured by determining a change in phase of the emitted light.

6. A method as claimed in any of claims 2 to 5 wherein the small change in absorption coefficient is induced by changing the wavelength of the light passed into the medium.

7. A method as claimed in claim 6 wherein the wavelength is changed by a few nanometres.

8. A method as claimed in any of claims 2 to 5 wherein the small change in absorption coefficient is induced by varying the concentration of chromophores in the scattering medium.

9. A method as claimed in claim 2 wherein the change in pathlength or phase is achieved by moving the light source and or the detector.

10. A method as claimed in any preceding claim comprising determining the modified scattering coefficient by measuring the intensity or phase or modulation depth of the light emitted from different locations in the medium.

11. Apparatus for determining an absorption coefficient or a scattering coefficient of a scattering medium, said apparatus being adapted and configured for use in the method of any preceding claims.

12. Apparatus for determining an absorption coefficient or a modified scattering coefficient of scattering medium comprising means for passing light (as herein defined) into the medium, means for detecting diffuse light emitted from the medium, means for causing a change in a parameter of the system formed by the apparatus and the medium, means for measuring resulting changes in at least two of the intensity, the phase (or transit time) thereof and the modulation depth of the emitted light, means for measuring said at least two changes, and means for determining said coefficient therefrom.

13. Apparatus for determining an absorption coefficient or a modified scattering coefficient of a scattering medium comprising means for passing light (as herein defined) into the medium, means for inducing a small change in the absorption coefficient or for producing a small change in the relative positions of a source and a detector of the light, means for measuring a resulting change in diffuse light emitted from the medium and means for determining the required coefficient from said resulting change.

14. Apparatus as claimed in claim 12 or claim 13 wherein the determining means determines the required coefficient from the ratio of two said resulting changes.

15. Apparatus as claim in claim 14 wherein the determining means determines the absorption coefficient from the ratio of the changes in intensity and transit time.

16. Apparatus as claim in claim 4 comprising means for varying the wavelength of the light by a small amount to induce the change in the absorption coefficient.

17. Apparatus as claimed in claim 16 wherein the means for passing light into the medium comprises a laser diode, the means for varying the wavelength comprising means for varying the operating temperature of the laser.

18. Apparatus as claimed in claim 16 wherein the means for passing light into the medium comprises a plurality of light sources having closely adjacent wavelengths, the means for varying the wavelength comprising means for switching selectively between said light sources.

19. Apparatus as claimed in claim 16 wherein the means for passing light into the medium comprises a source of white light, the means for varying the wavelength comprising means for selecting individually a plurality of closely adjacent wavelengths from the white light.

20. Apparatus as claimed in claim 11 wherein the light source and/or the detector is moveable and/or there are a plurality of light sources and/or detector at spaced apart locations.

21. A method or an apparatus for determining an absorption or coefficient or a modified scattering coefficient substantially as herein described with reference to the accompanying drawings.

The Patent Office

Application No:	GB 9605687.4	**Examiner:**	Bob Clark
Claims searched:	All	**Date of search:**	28 January 1997

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Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): G1A (AAMB, AAMX, ABAA, ABAG, ACDT, ACDX, ACEW, ACEX, ADMC, ADMX)

Int Cl (Ed.6): A61B 5/00; G01N 21/27, 21/31, 21/41, 21/45, 21/47, 21/49

Other: Online database: WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
	NONE	

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